Remarks

Favorable reconsideration is respectfully requested in view of the preceding amendments and the following comments.

The amendments to claim 1 are entirely editorial in nature. Amended claim 4 is effectively that claim in independent form. Amended claim 5 has merely changed the dependency of that claim so that it now depends from amended claim 4. New claim 21 corresponds to thrice amended claim 1 but is in "consist essentially of" terminology, thus excluding as an essential characteristic the very basis of Jain's Compass method. The more restrictive language excludes Jain's common skeleton base as an essential component.

Drawings

As set forth in the accompanying copy of the return postcard reflecting the filing of the application on March 12, 1999, there were four sheets of drawings. A copy of the first sheet of drawings as filed accompanies this response. A set of formal drawings (with an English translation of the Japanese text in Figures 3 and 4) is also submitted herewith.

Claim Objections

The objection to claims 3 to 5, 14 and 16 to 18 "under 37 C.F.R. 1.75(c)" is respectfully traversed. Claim 3 has been deleted. Claim 4 is presented in independent form, and claim 5 has been made dependent from amended claim 4. Issue is respectfully taken with the application of this objection to claims 14 and 16 to 18. Applicants submit that claim 14 further limits claim 1. In the event that the Examiner takes a contrary view, Applicants request that the Examiner point out on the record the basis in claim 1 for each of the limitations set forth in claim 14. Claim 16 further limits claim 14 by limiting the self-organizing neural network to a Kohonen neural network. Claim 17 further limits claim 16 to the manner in which the map is displayed. Claim 18 cannot possibly be an

improper dependent claim in view of the fact that it is an independent claim.

The rejection of claims 1 to 14, 16 to 18 and 20 "under 35 U.S.C. 103(a) as being unpatentable over Jain et al. in view of Satoh et al..." is also respectfully traversed. This ground of rejection is based on a combination of references with no direction or any basis of combining the references, much less in particular aspects of each attempted to be extracted solely on the basis for Applicants' claimed subject matter. The CAFC set forth current criteria for combining references and its opinion for *In re Lee*, 61 U.S.P.Q. 2d 1430 (Fed.Cir.2002), at 1433 and 1434:

> "The factual inquiry whether to combine references must be thorough and searching." It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. "[P] articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claim". The Examiner can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references". The Board rejected the need for "any specific hint or suggestion in a particular reference" to support the combination of the two references. Omission of a relevant factor required by precedent is both legal error and arbitrary agency action.

(1)Jain (J.Med.Chem. 1994):

(a) In the case of Jain, *the molecules to be compared with each other need to have a common skeleton* in the dominant part of the molecules.

(b)The Abstract of Jain describes that the method of Jain improves on previous techniques by automatically choosing conformations and alignments of molecules. Here, "conformations and alignments of molecules" is related to the common skeleton, and choosing "conformations and alignments of molecules" is done as follows.

In order to search for the common skeleton corresponding to the new molecule to be predicted the structure of the new molecule is given to "the final model (please see Fig. 1 of Jain)", and *the new molecule to be predicted is superposed on the common skeleton in "the final model"*. After the common skeleton corresponding to the new molecule to be predicted

is found out in "the final model", the un-overlapped portion of the new molecule, which does not overlap with the common skeleton, is specified.

In the next step, the un-overlapped portion of the new molecule is analyzed by using the molecular surface representation of a molecule's three-dimensional structure.

(c) The Examiner states in the office Action that this molecular surface representation of a molecule's three-dimensional structure of Jain is similar to the steric factor derived from van der Waals energies in the frontier surrounding surface in the present invention.

However, as mentioned above, in order to predict the activity of the new molecule, it is absolutely necessary in Jain's method that there is a common skeleton between the new molecule to be predicted and the molecules in "the final model".

Thus, *it is not possible in Jain's method* to determine the degree of similarity between the new molecule to be predicted and the molecules in "the final model" *when the new molecule to be predicted has quite a different size and has no common skeleton with the molecules in "the final model".*

(d) On the other hand, it is not necessary for the present invention to have a common skeleton in order to predict the activity of the new molecule. *The present invention has no relation with whether a new molecule has a common skeleton or not.* Therefore, Jain's method is very different from the present invention.

(e) In the field of development of medicines, the cooperative molecular field analysis (CoMFA) method is conventionally known as a method for predicting the activity characteristics of ligand molecules. Here, Jain can be said to belong to "CoMFA" in the sense that a common skeleton is necessary as a common portion in the molecules to be compared, and the common skeleton is the dominant part of the molecules.

In Jain's method, one CoMFA field is obtained *for the whole molecule, not for each site of the molecule*, because the existence of the common skeleton is always assumed.

On the other hand, in the present invention, the molecule to be predicted is decomposed into minute sites in the procedure of prediction in order to derive characteristic

values for each site, *and it may be possible to obtain the reacion characteristic for each site*. Therefore, *it is possible to know to what degree each site of the molecule contributes to the reaction characteristic of the whole molecule* , and it is possible to accurately predict the reaction characteristics of the molecule.

(f) In addition, *Jain's method is mainly applied to the prediction of activity and the design of a medicine in the development of the medicine, because the existence of the common skeleton is assumed.* Jain's method cannot be applied to the prediction of reactivity and the design of synthesis in the field of synthetic chemistry, because the existence of the common skeleton is difficult to be assumed in the field of synthetic chemistry.

It should be noticed that it is necessary to predict various reaction characteristics of the molecules having no common skeleton with each other in the field of synthetic chemistry.

(g) As mentioned above, in the case of Jain, the skeleton needs to be common between the two molecules to be compared. In Jain, the two molecules to be compared are positioned so that the two skeletons are superimposed in the rectangular coordinate space where lattice points are distributed as probe points.

The procedure in the present invention is very different from the case of Jain. In the case of the present invention, for example, there is no procedure of positioning two molecules to be compared in order to superimpose two molecules, and there is no need to set lattice points distributed as probe points in the rectangular coordinate space.

(2) Satoh (J.Chem.Inf.Comput.1998, 38, 210-219):

Satoh is a paper written by the present inventor and she understands the paper very well.

(a) The Examiner states that Satoh discloses a method of building a reaction map of molecules and using a neural network to classify the reaction of molecules.

However, the information disclosed in Satoh is not the most essential features of the present invention.

The essential features of the present invention exist in building the reaction characteristic values composed of three factors: the space occupied rate, the electrostatic

value, and the steric factor. These features are not at all disclosed in Satoh.

(b) The Examiner also states that Satoh states "the constructed reaction map will be employed for solving problems in computer-assisted reaction prediction and synthesis design".

However, Satoh does not disclose *anything concrete* as to how to predict the reaction characteristic of a new molecule.

(c) Therefore, even if Jain and Satoh were combined, the present invention could not be motivated or even reconstructed.

The characteristic features of the present invention can be understood by comparing it with the prior art described in the text of the specification (page 1, line 27, to page 3, line 17). In that regard *Jain can be said to belong to "CoMFA" in the sense that a common skeleton is necessary as a common portion in the molecules to be compared and the common skeleton is the dominant part of the molecules.*

"In the field of development of medicines, the cooperative molecular field analysis (CoMFA) method is conventionally known as a method for predicting the activity characteristics of ligand molecules (see, e.g., R.D.III Cramer, et al., J. Am. Chem. Soc., 1988, 110, 5959).

In the CoMFA method, a CoMFA field is produced to give the three-dimensional expression of a chemical structure of ligand molecule. The CoMFA field is derived by forming, e.g., a rectangular parallelepiped-shaped region surrounding a molecule, the activity characteristic of which is to be predicted, *considering lattice points, which are distributed in the surrounding region in the form of a lattice, as probe points*, and putting probe atoms at the respective probe points to calculate energy of the interaction between the probe atoms and the components of the molecule, such as substituents.

In the CoMFA method, it is assumed that a portion occupying a major part of a molecule, the reaction characteristic of which is to be predicted, is *a common skeleton serving as a common portion*, and *the substituted portions of molecules having a common skeleton are substituted by various substituents.* On the basis of the correlation

characteristics of the obtained CoMFA, the presence of similarity between activity characteristics of *the molecules having the common skeleton is determined.*

However, in the CoMFA method, it is assumed that the molecules have the common skeleton, and when the prediction of the activity characteristic of a certain molecule is intended, the presence of similarity between activity characteristics *is determined only between the certain molecule and another molecule having a common skeleton with the certain molecule.*

Thus, it is not possible to determine the presence of similarity between reaction characteristics of molecules, which have quite different sizes and which do not have any common skeleton.

In addition, in the CoMFA method, a molecule, the reaction characteristic of which is to be predicted, *is not decomposed into minute sites to derive characteristic values for each site,* and one CoMFA field is obtained *as the whole molecule. Therefore, it is not known how each of the sites of the molecule contributes to the reaction,* so that it is not possible to accurately predict and consider the reaction characteristics of the molecule.

Moreover, in the CoMFA method, the rectangular parallelepiped surrounding the overlapped ligand molecules varies with the size of a target ligand molecule group, so that there is a limit that the obtained characteristic value depends on the target ligand molecule group.

In addition, the CoMFA method is applied to the prediction of activity and the design of a medicine in the development of the medicine, so that *the CoMFA method cannot be applied to the prediction of reactivity and the design of synthesis in the field of synthetic chemistry.* There is no reaction characteristic predicting method serving as a guide to the prediction of reactivity and the design of synthesis in the field of synthetic chemistry and as a guide to the prediction of activity and the design of a medicine in the development of the medicine.

"It is therefore an object of the present invention to eliminate the aforementioned problems and to provide a molecular reaction characteristic predicting method, which can

be applied to a wide field of chemistry, including the field of synthetic chemistry, as well as the field of development of medicines and which can accurately predict the presence of similarity between reaction characteristics of various molecules *without limitations on common skeleton*, and a reaction characteristic predicting map and computer-readable storage medium."

Having overcome all grounds of rejection, favorable action on the merits is now in order and early action toward that end is respectfully solicited.

Respectfully submitted,

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